Introduction
Cancer is responsible for 25% of deaths in the developed countries. In addition to surgical resection of tumour tissue, cancer treatment often involves adjuvant or neo-adjuvant radiotherapy and chemotherapy to kill residual cancer cells by programmed cell death (apoptosis) after surgery. Effective radiotherapy and chemotherapy treatment programmes are those that kill cancer cells while minimising the harmful secondary effects caused by the therapy.

Technology
Aware of the need to personalise cancer treatment programmes in order to more effectively kill cancer cells while preserving healthy tissue, researchers at RCSI have developed a Dose Response Medical Outcome Model Predictor System (DR_MOMP). This patented computerized model using insights obtained from research in the field of translational systems biology to provide a fast method of determining the sensitivity of an individual patient’s cancer cells to genotoxic stress or other stressors (such as death receptor activation and tyrosine kinase inhibition) that are induced by current radio- or chemotherapy treatment. DR_MOMP works by analysing patient specific BCL-2 protein family profiles (BAK, BAX, BCL2, BCL(X) and MCL1) obtained from biopsies or resected tumour material and calculates the minimal ‘stress dose’ that is required to lead to mitochondrial outer membrane permeabilisation (MOMP), the key event for apoptosis initiation.

Applications
- Reducing drug development risk: Most novel anti-cancer drugs tested in classical trials fail late (at phase II or III), with associated enormous costs (typically >$500 million). Failure is often due to poor in vivo efficacy, possibly from suboptimal treatment schedules or dosing, DR_MOMP can evaluate novel drugs and treatment schedules a priori through performing in silico trials.

- Stratifying patients in clinical trials: DR_MOMP can quickly assess the potential benefit of novel BCL-2 antagonists (such as ABT263, ABT37, Obatoclax and ApoG2) in the treatment of individual cancer patients and hence can be applied as a stratification tool in clinical trials. In addition, DR_MOMP can identify patients who are not benefiting from today common used therapy or are of risk of recurrence.

- Personalising chemotherapy treatment: DR_MOMP can determine patient specific responses to radio- and chemotherapy resulting in a more accurate calculation of the “therapeutic window” for individual patients.

Figure 1: DR_MOMP informs Stage 2 Cancer patient treatment
Stage II CRC patients with a “DR_MOMP predictor result” above the threshold have a significant lower overall survival (OS) compared to patients with a “model predictor result” below the threshold allowing identification of Stage II patients who can benefit from adjuvant chemotherapy after resection.

Figure 2: DR_MOMP informs Stage 3 Cancer patient treatment
DR_MOMP can predict survival (Panel A - OS) and disease free survival (DFS) of Stage III cancer patients (Panel B) and works independently of different factors such as the tumour extend/size (Panel C &D) or KRAS gene mutation (Panel E &F).

Advantages
Instead of using single genes or proteins as markers, DR_MOMP uses more valuable insights obtained from topological analysis of cell death protein signalling pathways to design cancer treatment paradigms and predict clinical outcomes. In addition, by using individual patient protein expression information as input, DR_MOMP enables the personalisation of individual patient treatment and dosage programmes, thereby ensuring the best clinical for each individual patient.